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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	)	
ATSUMI et al	)	
Serial No.: 07/036,124	)	Art Unit: 128
Filed: April 7, 1987	)	Examiner: Robert J. WARDEN
For: NEW CEPHALOSPORIN COMPOUNDS AND THE PRODUCTION THEREOF	)	

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C.

Sir:

KUNIO ATSUMI, being duly warned, deposes and says that:

He is a citizen of Japan, residing at No. 3-16-11, Hiyoshi, Kohoku-ku, Yokohama-shi, Kanagawa-ken, Japan.

He is by profession a chemist, graduated Graduate School of Science and Technology, University of Tokyo Institute of Technology in March, 1979 and having received the degree of Ph. D. from University of Tokyo Institute of Technology.

Since April, 1979, he has worked for Meiji Seika Kaisha, Ltd. as an organic chemist working principally in the field of cephalosporins and related antibiotics.

He is the author or co-author of some 15 publications and an inventor or co-inventor of 8 pending

Japanese patent application and several foregin patent applications.

He is a member of the following technical and scientific societies:

Chemical Society of Japan.

Pharmaceutical Society of Japan.

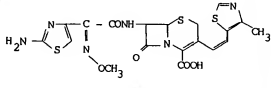
The subject U.S. application is a continuation application of the U.S. application Serial No. 06/769,746 fild August 7, 1985.

He has read the Office Action dated February 4, 1988 in the subject U.S. patent application, of which he is a co-inventor, as well as the references cited therein.

In order to supplement the applicant's declaration under 37 CFR 1.132 filed October 12, 1986 for the U.S. patent application SN. 06/769,746, and in order to distinguish the antibacterial activity possessed by the compounds of the present invention, especially the compounds of formula (Ic) of the claim 4 and the particular compounds of the claim 19 of the subject U.S. application over the known similar cephalosporins of U.S. patent No. 4,307,116 of Farge et al (the cited reference B) which are similar to the compounds of the present invention in respect of the nature of the 7-position substituent but are different from the compounds of the present invention

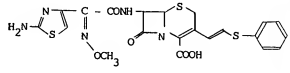
in respect of the nature of the substituent on the 3-position thiovinyl group, as well as over the known cephalosporins of U.S. patent No. 4,255,423 of Beattie et al (the cited reference A) which are similar to the compounds of the present invention in respect of the nature of the substituted vinyl group at the 3-position but are different from the compounds of the present invention in respect of the nature of the 7-position substituent, the following comparisons were conducted between them by determining the values of the minimum inhibitory concentrations (MIC) against gram-positive bacteria and gram-negative bacteria of the compounds listed in the following Table 1.

Table 1

Test Compounds	Nomination and Structure
Compound A according to the present invention, as claimed in the claim 19 and as embraced by the compounds of the claim 4 of the subject U.S. patent application	7-{2-methoxyimino-2-(2-amino-thiazol-4-yl) acetamido}-3-{2-(4-methylthiazol-5-yl) vinyl}-3-cephem-4-carboxylic acid (syn-isomer, (Z)-isomer, i.e. cis-isomer) of the formula 

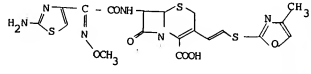
Compound E (Comparative, the compound of Example 2 of U.S. patent No. 4,307,116 of Farge et al)

7-{2-methoxyimino-2-(2-amino thiazol-4-yl)acetamido}-3-{ 2-phenylthiovinyl}-3-chephem -4-carboxylic acid (syn-isomer, mixture of the (E)- and (Z)- isomers) of the formula



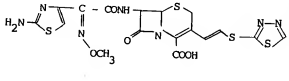
Compound F (Comparative, the compound of Example 40 of U.S. patent No. 4,307,116 of Farge et al)

7-{2-methoxyimino-2-(2-amino thiazol-4-yl) acetamido}-3-{2-(4-methyl-oxazol-2-yl) thiovinyl}-3-cephem-4-carboxylic acid (syn-isomer, (E)-isomer, i.e. trans-isomer) of the formula



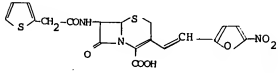
Compound G (Comparative, the compound of Example 49 of U.S. patent No. 4,307,116 of Farge et al)

7-{2-methoxyimino-2-(2-amino thiazol-4-yl)acetamido}-3-{2-(1,3,4-thiadiazol-2-yl) thiovinyl} -3-cephem-4-carboxylic acid (syn-isomer, (E)-isomer, i.e. trans-isomer) of the formula



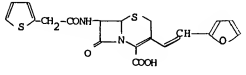
Compound H (Comparative, the compound of Example 6 of U.S. patent No. 4,255,423 of Beattie et al)

7-(2-thienylacetamodo)-3-{2-5-nitrofuryl)vinyl}-3-cephem-4-carboxylic acid ((Z)-isomer, i.e. cis-isomer) of the formula



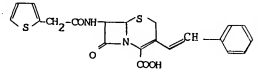
Compound I (Comparative, the compound of Example 7 of U.S. patent No. 4,255,423 of Beattie et al)

7-(2-thienylacetamido)-3-(2-furylvinyl)-3-cephem-4-carboxylic acid of the formula



Compound J (Comparative, the compound of Example 16 of U.S. patent No. 4,255,423 of Beattie et al)

7-(2-thienylacetamido)-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid of the formula



Compound A as above according to the present invention is representative of the compounds of the present invention and is the one as produced in Example 10 of the subject U.S. patent application and covered

by the compound of the formula (Ic) according to the claim 4 and specifically set out in the claim 19 of the subject U.S. patent application.

The MIC. values of these Compounds A, E, F, G, H, I and J were determined according to a standard serial dilution method by incubating the test organisms in "Sensitivity disk of agar-N" (a product commercially available from Nissui Co., Ltd., Japan) as an incubation medium at 37°C for 20 hours (overnight). The antibacterial spectra (MIC.) of the tested compounds so determined are shown in Table 2 below,

Table 2

Test organisms	MIC. value (μ/mℓ) Test compounds A	E	F	G	H	I	J
Gram-positive bacteria							
Staphylococcus aureus 209P JC-1	0.20	0.39	0.78	0.39	12.5	0.20	0.05
Staphylococcus epidermidis ATCC 14990	0.39	0.78	1.56	0.39	6.25	0.39	0.20
Gram-negative bacteria							
Escherichia coli W3630 RGN14	0.39	1.56	0.78	0.39	>100	>100	>100
Klebsiella oxytoca F-0100	1.56	12.5	25	50	>100	>100	>100
Proteus vulgaris GN76/C-1	0.39	0.39	0.78	0.78	>100	>100	>100
Pseudomonas aeruginosa GN10362	25	50	100	100	>100	>100	>100
Pseudomonas aeruginosa M-0148	25	100	100	>100	>100	>100	>100

From the comparisons between the results of Table 2 above, it can be observed that Compound A of the present invention is remarkably superior to or is comparable to the comparative Compounds E, F, and G of Farge et al in respect of their antibacterial activity against the tested totally seven species of both the gram-positive bacteria and the gram-negative bacteria, and that Compound A of the present invention shows a remarkably higher activity against the tested five species of the gram-negative bacteria, over the comparative Compounds H, I and J of Beattie et al, and that although Compound A is comparable to or inferior to the Compound I and J for the antibacterial activities against the tested two species of the gram-positive bacteria, Compound A of the present invention is able to exhibit remarkably improved antibacterial activities against the tested two species of the gram-positive bacteria over the comparative Compound H of Beattie et al. This reveals that Compound A of the present invention is an excellent antibacterial agent which is much more greatly valuable in therapeutic treatments of bacterial infections, as compared to the comparative Compounds E, F, G, H, I and J tested.

Besides, the excellent characteristic that the representative Compound A tested as above according to

the present invention is able to exhibit the remarkably high antibacterial activities against a wide range of the bacterial species, including both the gram-negative bacteria and the gram-positive bacteria is common to all the compounds of the present inventions, as has been demonstrated in Table 1 on page 28 of the specification of the subject U.S. patent application which shows the MIC values (μ/mℓ) of the particular compounds of Examples 10-16, 18, 21 and 30-34 of the subject application. That this excellent characteristic exhibited by the compounds of the present invention is remarkable and surprising in view of that the G.L. Dunn's article on pages 1-10 of the "Journal of Antimicrobial Chemotherapy" (1982) 10, Suppl. C. 1-10 (the cited reference R of Dunn) has stated on page 2 lines 15-17 to the effect that the third-generation cephalosporins, including Cefotaxime, Ceftizoxime, Cefmenoxime, Ceftriaxone, Ceftazidime, Cefoperazone and Moxalactam (all of these agents containing the aminothiazolyloximino substituent at the 7-position commonly to the compounds of the present invention) tend to be less active than cephalosporin compounds of the earlier, first and second generations against gram-positive bacteria, most notably Staphylococcus aureus, with reference to the comparative in-vitro activity data (MIC) of Ceftizoxime (one of the third-generation), Cefamandole (one of the

second-generation) and Cephalothin (one of the first-generation) as shown in Table II on page 2 of the cited reference of Dunn. It is therefore surprising that the representative Compound A as tested of the present invention and the other compounds of the present invention are able to exhibit not only the remarkably high antivacterial activity of the MIC value of 0.78 μ/mℓ or less especially against Staphylococcus aureus, one of the gram-positive bacteria, but also the remarkably high antivacterial activities of the MIC values of 0.39 μ/mℓ or less against many of the gram-negative bacteria species. These excellent antibacterial properties of the compounds of the present invention, especially represented by Compound A as tested above are not predictable from the teaching of the cited reference of Farge et al and the teaching of the cited reference of Beattie et al, either alone or even in combination, I consider.

In addition, the compounds of the present invention are more highly absorbable through the intestines of a living animal when orally administered in the form of their esters with an enzymatically cleavable alcohol, as compared to the compounds of the cited reference of Farge et al and the compounds of the cited reference of Beattie et al. In order to demonstrate this, I and

associated biologists further repeated the experiments described on page 32 line 15 to page 34 line 15 of the specification of the subject U.S. patent application, with using the pivaloyloxymethyl esters of Compound A, E, F, G, H, I and J as prepared by us.

We repeated the experiments by the test procedure and the test conditions exactly same as described in Test 1 of on pages 33-34 of the specification of the subject U.S. patent application. The test results obtained are shown in Table 3 below.

Table 3

Test Compound	Rate of recovery of the test compound (in the free carboxylic acid form) in urine (%)
Pivaloyloxymethyl ester of Compound A according to the present invention	20%
Pivaloyloxymethyl ester of Compound E (comparative)	9.6%
Pivaloyloxymethyl ester of Compound F (comparative)	6.2%
Pivaloyloxymethyl ester of Compound G (comparative)	7.1%
Pivaloyloxymethyl ester of Compound H (comparative)	0.9%
Pivaloyloxymethyl ester of Compound I (comparative)	2.5%
Pivaloyloxymethyl ester of Compound J (comparative)	0.3%

The higher the rate of recovery of the test compound in the urine, the more the test compound as orally given is absorbable through the intestines of the animal treated and the more the antibacterial potency of the test compound is maintainable to a substantial extent in the body of the animal until it is excreted in the urine, without receiving a substantial degradation of the cephalosporin compound in vivo. From the results of Table 3 above, therefore, it is noticeable that Compound A of the present invention is remarkably superior to the comparative Compounds E, F, G, H, I and J as an orally administrable antibacterial agent in that Compound A is more absorbable into the body of the animal through the intestines and is able to give a higher potency of the test compound (Compound A) in the blood for a prolonged time and to achieve its antibacterial power, as compared to the comparative Compounds E, F, G, H, I and J, until it is excreted into the urine.

I consider that the higher absorbability through the intestines of the pivaloyloxymethyl ester of the tested Compound A and hence of the compounds of the present invention is never predictable from the teaching of the cited reference of Farge et al and the teaching of the cited references of Beattie et al, even in combination

with the teachings of the another cited references of Berger, Furlenmeier and Dunn, where no reference is made at all to the improvement in the absorbability of the orally administered cephalosporins through the intestines of the animal.

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Done at Yokohama, Japan, this 28th day of April, 1988

KUNIO ATSUMI

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